DRUG RESEARCH AND DEVELOPMENT

The discovery of sulfanilamide, penicillin, and other antibiotic drugs in the early 20th century revolutionized the treatment of infectious diseases and gave doctors powerful new tools that for the first time allowed them to easily defeat bacterial infections that would otherwise have been life-threatening. More recently, drugs have been developed that can combat viruses such as influenza and HIV, as well as fungal and parasitic infections. Unfortunately, many infectious agents have become resistant to current therapies, thereby threatening to destroy the effectiveness of these original "wonder drugs." Also, the immune system can itself cause illnesses such as diabetes, arthritis, and multiple sclerosis when it inappropriately attacks the body's own tissues.

The development of new therapies for the treatment of infectious and immune-mediated diseases is therefore one of NIAID's highest priorities. Basic research is the foundation for drug development. Through scientific advances in microbiology, virology, and immunology, scientists identify potential targets for therapeutic agents and new strategies for treating infectious and immune-mediated diseases. Often in collaboration with industry, academia, and other government agencies, NIAID carries out many research programs that facilitate drug development and helps maintain related resources, including databases of chemical structures that can be screened for use as therapeutic agents, facilities to conduct preclinical testing of promising drugs, and clinical trial networks to evaluate the safety and efficacy of drugs and therapeutic strategies. Because drug development is a key component of NIAID's mission, each NIAID Division is actively involved in the drug development process.

Division of Acquired Immunodeficiency Syndrome

The Division of Acquired Immunodeficiency Syndrome (DAIDS) devotes a substantial portion of its resources to the discovery and development of new therapies and/or treatment strategies for people with HIV/AIDS, including treatments for AIDS-associated opportunistic infections (OIs) and co-infections, as well as complications of antiretroviral therapy. The goal of DAIDS' therapeutics research effort is to foster the discovery and development of treatments to improve the quality and duration of life of HIV-infected individuals. To fuel the drug discovery and development pipeline, NIAID awards investigator-initiated research grants as well as grants and contracts in targeted areas addressed through various program solicitations.

A strong portfolio of basic research is the foundation for DAIDS drug development activities. Over the past 16 years, drug discovery efforts have concentrated on a relatively small number of HIV targets, especially reverse transcriptase (RT), the enzyme that makes a DNA copy of the viral RNA genome after it invades a cell, and protease (PR), the enzyme that activates immature HIV precursor proteins.

A combination of RT and PR inhibitors known as highly active antiretroviral therapy, or HAART, has revolutionized the treatment of people with HIV, successfully suppressing the virus and decreasing the incidence of opportunistic infections in many people in developed countries. These drugs, however, do not constitute a magic bullet. Many patients suffer metabolic abnormalities and toxicities, and some have difficulty adhering to the complex drug regimens required. Strains of HIV that are resistant to therapy can also emerge.

Fortunately, new classes of therapeutic agents have recently entered the development pipeline. Some of these interfere with virus binding and entry into the cell, while others act on viral

targets such as HIV integrase, an enzyme that incorporates the HIV genome into a host cell's DNA. Stopping HIV before it integrates into a host cell is an attractive strategy because it would potentially protect healthy cells from infection and thereby prevent immune system dysfunction. Therapeutic vaccines, which attempt to spur the immune system of an infected person to mount a more vigorous defense, are a potential immunologic approach to complement drug treatment. Even as these advances continue, so too, does the need for discovering new host and viral targets, novel drugs and delivery systems, and immunologic approaches to address the dual problems of drug resistance and toxicity.

The pathways that lead to new HIV drug therapies are many and varied, but all begin with basic research. The research includes studies of the structure and function of viral and cellular proteins critical to the HIV life cycle, immunopathogenic studies to understand how the virus disables the immune system, genetic studies—both human and viral—to define which genes affect susceptibility to infection and disease progression, and studies to understand how to restore effective immune function.

DAIDS pursues these approaches to targeted drug discovery through investigator-initiated grants, Small Business Innovation Research grants, and contracts. Currently, DAIDS is supporting the Novel HIV Therapies: Integrated Preclinical/Clinical Program (IPCP). The IPCP supports the preclinical evaluation, development, and pilot-stage clinical study of novel agents and strategies to suppress HIV replication, interfere with disease progression, reconstitute or repair immune system damage, genetically protect cells against HIV, and ameliorate the consequences of infection. Once a novel therapeutic is identified and moves into preclinical development, it is systematically varied in small ways in an effort to improve its overall activity, safety, and effectiveness. These variations on a theme are subjected to additional *in vitro* testing, evaluating the agent's activity against a range of HIV isolates in different cell lines and animal models. If appropriate, the IPCP supports early clinical evaluation in human studies.

DAIDS provides contract resources for *in vitro* and *in vivo* screening and testing and evaluation of potential therapeutic compounds. DAIDS has an in-depth array of resources available to investigators to evaluate novel synthetic compounds and purified natural products as anti-HIV, anti-OI, and anti-tuberculosis (TB) therapies, as well as topical microbicides. Also offered are resources to assess therapies for their effects on immunologic functions. DAIDS offers assistance with animal model evaluation of novel antiviral, anti-infective, anti-tubercular, immune-based therapies and topical microbicides in a number of animal models, including rodents, dogs, and nonhuman primates. Potential therapies can also be evaluated for effects on immunologic parameters as a component of animal efficacy studies. Extensive toxicology and pharmacology testing can be conducted to aid in the evaluation of promising anti-HIV agents, anti-infectives, immune-based therapies, and topical microbicides. DAIDS' focus is on assisting investigators in fulfilling the current testing requirements necessary for Investigational New Drug (IND) application filing. An array of chemistry, formulation, and manufacturing resources are available to assist investigators. Each of these services can be performed under Good Laboratory Practice and Good Manufacturing Practice conditions. DAIDS can also facilitate access to clinical virology, immunology, and pharmacology research laboratory evaluations; provide laboratory assay protocols; and aid in developing new diagnostic and therapeutic monitoring methods. Contract resources are also devoted to supporting clinical research on therapeutic interventions for *Mycobacterium tuberculosis (M.tb)* infection and co-infection with HIV (see *www.taacf.org*). This support includes high-throughput screening of anti-*M.tb* compounds and testing in animal models. For

additional information on *M.tb* research, see the "Tuberculosis" section on page 133.

DAIDS also supports therapeutics discovery and development by helping to acquire, share, and disseminate resources for promising treatments for treating HIV infection and associated opportunistic pathogens. To assist investigators during initial research design, DAIDS created and maintains computerized databases of compounds screened for anti-HIV, anti-infective, and anti-TB activity. The databases were established to monitor developments in the chemotherapy of HIV and OIs, to track compounds for further study, and to serve as an information source. They contain chemical structures, *in vitro* efficacy and cellular cytotoxicity test results, as well as *in vitro* and *in vivo* resistance data. The anti-HIV database contains more than 15,000 compounds; the anti-TB database, nearly 50,000 compounds; and the anti-OI database, greater than 10,000 compounds. DAIDS also has access to other chemical and biological databases containing information on more than 500,000 additional compounds. The Division's scientific research staff is available to assist in accessing nonproprietary information contained in these databases and to help guide drug discovery and development efforts. References in the scientific literature are also available. For more information on the anti-HIV and anti-OI drug databases, visit *http://chemdb2.niaid.nih.gov/struct_search/default.html*.

Additionally, the NIH AIDS Research and Reference Reagent Program provides state-of-the-art biological and chemical materials for the study of HIV and related opportunistic pathogens. These reagents are available to registered users worldwide at no cost. The AIDS reagent program also serves as an information resource for scientists, a liaison to communicate the needs of investigators in establishing research partnerships, and a provider of technical assistance on handling and shipping infectious substances. Additional information is available at *www.aidsreagent.org*.

The evaluation of new drugs and therapeutic agents in people is a critical aspect of the DAIDS therapeutics research agenda. These clinical studies define which new agents are effective against HIV and its associated complications and also clarify how best to use these drugs. During the past decade, DAIDS-sponsored therapeutics research has already had a dramatic impact on understanding the pathogenesis and clinical management of HIV infection. Clinical trials research networks funded by DAIDS have defined guidelines for (1) the treatment of primary HIV infection and associated opportunistic infections, (2) prophylaxis of secondary infections, (3) measurement of biological markers, such as CD4+ counts and viral load for predicting a drug's effectiveness and disease progression, and (4) the use of antiretroviral drugs for preventing mother-to-infant transmission. DAIDS-supported clinical trials programs can address treatment research questions in a variety of different patient populations. Therapeutic candidates (or combination therapies) that fit the mission and focus of these programs may qualify for testing in phase I, II, and III trials. Currently the DAIDS-sponsored therapeutics clinical trial networks include the Adult AIDS Clinical Trials Group, the Pediatric AIDS Clinical Trials Group, and the Terry Beirn Community Programs for Research on AIDS.

NIAID is now in the process of restructuring all of its clinical trials networks to improve the coordination, efficiency, and flexibility of its research networks. Over the past 2 years, DAIDS has worked diligently with its stakeholders and advisory committees to address these issues, delineate six high-priority areas of clinical science, and develop new organizational and managerial strategies to support NIAID's HIV/AIDS clinical research agenda. In restructuring the HIV/AIDS clinical trials networks, NIAID

seeks to stimulate new collaborative approaches; leverage the networks' substantial complementary strengths and resources; and coordinate HIV/AIDS prevention, vaccine and therapeutic research across multiple study participant/patient populations (e.g., age, gender, ethnicity, risk factors). Awards for the new Leadership for HIV/AIDS Clinical Trials Networks are planned for 2006, while awards for the new Clinical Trial Units are planned for early 2007.

Division of Microbiology and Infectious Diseases

The Division of Microbiology and Infectious Diseases (DMID) supports the discovery and evaluation of new drugs for infectious diseases at all three phases of the process: discovery (disease pathogenesis, target identification, characterization, and screening), preclinical evaluation (testing of human infections in animal models), and clinical evaluation (evaluation of new therapies). Because DMID's mandate encompasses a broad array of infectious diseases, the Division's drug development efforts address the entire spectrum of infectious diseases, including hepatitis, herpes, TB, sexually transmitted infections, malaria, fungal diseases, viral respiratory infections, hospital-associated bacterial infections, and pneumonia. Moreover, the Division's activities support all stages of drug discovery and development, from the test tube to the bedside and, especially for animal model and clinical research, involve close collaborations with the pharmaceutical industry and the Food and Drug Administration (FDA). Finally, in FY 2005, DMID supported approximately 40 large-scale genome-sequencing projects; the genomic information obtained has great potential for further advancing the discovery and evaluation of new therapeutic agents for infectious diseases.

Discovery and Preclinical Evaluation

DMID-funded research includes basic research on molecular targets, molecular modeling, drug design and synthesis, and mechanisms of resistance, as well as the development of advanced spectrometric technologies for obtaining higher resolution structural information. This work is supported primarily through the investigator-initiated research program. DMID supports basic and applied research on the discovery and design of antiviral agents; these projects have led to the design of new drugs for influenza, cytomegalovirus (CMV), poxvirus, and hepatitis. Preclinical evaluations of antiviral therapies also are conducted in animal models of human viral infections. In FY 2005, experiments in a mouse model showed that an antiviral drug currently used against annual influenza strains also can suppress the deadly influenza virus that has spread from birds to humans. Since early 2004, this avian flu virus has killed more than a hundred people in Southeast Asia and the Middle East.

DMID maintains an active antiviral screening program that tests potential antiviral agents *in vitro* for activity against many different viruses, including herpes simplex viruses (HSV-1, HSV-2, varicella-zoster virus, Epstein-Barr virus, CMV, human herpesvirus [HHV]-6, HHV-8); respiratory viruses (influenza A and B, respiratory syncytial virus, parainfluenza virus, measles, rhinovirus, adenovirus, sudden acute respiratory syndrome coronavirus); hepatitis B and C; papillomaviruses, BK virus, orthopoxviruses (vaccinia and cowpox); and other viruses that cause hemorrhagic fevers and encephalitides, including West Nile virus. DMID also collaborates with the U.S. Army Medical Research Institute on Infectious Diseases antiviral program in the search for therapies for exotic viruses such as Ebola and Sin Nombre. DMID and DAIDS staff members also interact closely on drug discovery research and therapeutic evaluation efforts for HIV therapies.

Basic research on pathogen replication has led to the identification of new therapeutic targets for viruses, bacteria, and parasites, which in turn opens up new possibilities for the development of drugs that attack these targets. DMID

continues to fund research on the development of new methods and improvement of existing ones for the therapeutic treatment of malarial infections. Projects include identification and characterization of unique parasite pathways that can serve as targets for drugs, determination of the mode of action of existing and potential drugs, and analysis of the mechanisms by which parasites have become resistant to existing drugs.

The emergence of antibiotic-resistant pathogens, including those that cause pneumonia and TB, has become a serious global health threat. Methicillin-resistant *Staphylococcus aureus*, for example, has rapidly emerged as a community-associated infection, and in two separate instances *S. aureus* has acquired genes that make it resistant to the powerful antibiotic vancomycin. Public health officials fear that a strain of *S. aureus*—or some other pathogen—might arise that resists all antibiotics currently available.

In response, the Public Health Service, under the leadership of the NIH, FDA, and the Centers for Disease Control and Prevention (CDC), developed an antimicrobial resistance action plan that provides a blueprint for specific, coordinated government actions to address the emerging threat. The four areas of emphasis are (1) surveillance, (2) prevention and control, (3) research, and (4) product development. NIAID has the lead in the area of research. The original plan, *A Public Health Action Plan to Combat Antimicrobial Resistance, Part 1: Domestic Issues,* as well as the annual progress reports and activity inventory, are available online at *www.cdc.gov/drugresistance/actionplan*. In June 2005, the Interagency Task Force on Antimicrobial Resistance hosted a public meeting to discuss progress in implementing the multi-agency action plan. The task force is cochaired by the NIH (NIAID), CDC, and FDA and includes broad Federal agency representation.

Prompt and accurate diagnosis of an infection is obviously important for good patient care, because it allows doctors to choose the right antibiotic. But good diagnostic tools also help to preserve the efficacy of current therapies by helping to limit the exposure of pathogens to inappropriate treatments and aiding in the identification of patient populations for the evaluation of new antimicrobial agents. In FY 2005, DMID awarded nine grants through a new research initiative called "Sepsis and CAP: Partnerships for Diagnostics Development," which supports industry development of broad diagnostic technologies for early detection of major causes of septicemia, bacteremia, candidemia, and community-acquired pneumonia.

Clinical Studies

DMID supports clinical research with both individual grants and contract-supported programs such as the Collaborative Antiviral Study Group (CASG). The CASG, supported by a single award to the University of Alabama at Birmingham, is a multi-institute, collaborative network composed of more than 60 institutions under which clinical studies of therapies for viral infections are conducted. For example, the CASG supports clinical trials that assess the safety and efficacy of an experimental immunoglobulin treatment for West Nile virus encephalitis and help to elucidate its natural history. For more information about the CASG, visit *www.niaid.nih.gov/daids/pdatguide/casg.htm*.

The NIAID Mycoses Study Group (MSG), funded by both DMID and DAIDS, has supported clinical trials of antifungal therapies for opportunistic and endemic mycoses (fungal infections) since the 1970s. In early 2001, in conjunction with the scheduled completion of the MSG contract, two contracts were awarded: the Bacteriology and Mycology Study Group (BAMSG) and the Bacteriology and Mycology Biostatistical and Operations Unit (BAMBU). The BAMSG continues to conduct clinical trials of interventions for serious fungal diseases as well as healthcare-associated resistant bacterial

infections. The BAMBU provides biostatistical and administrative support for these clinical trials.

Also, NIAID is sponsoring a trial to test the effectiveness of two infection control strategies for reducing methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* colonization and infection in intensive care units. The Strategies to Reduce Transmission of Antimicrobial Resistant Bacteria in Intensive Care Units (STAR*ICU) Trial involves 20 hospitals working in collaboration with the NIH Clinical Center.

Other DMID-supported research groups that conduct drug and vaccine evaluations as part of their overall mission include the Vaccine and Treatment Evaluation Units, the International Centers for Infectious Diseases Research, the Sexually Transmitted Diseases (STD) Cooperative Research Centers, and the STD Clinical Trials Unit. NIAID is conducting a phase III efficacy trial using the STD Clinical Trials Unit to determine whether azithromycin, a drug approved for treatment of other infections, is as effective for early syphilis therapy as the usual penicillin treatment; this trial continues to enroll patients. In FY 2003, NIAID launched a pivotal phase III double-blind clinical efficacy trial of an investigational vaccine for the prevention of genital herpes. This trial has expanded from 25 sites to more than 40 sites across the United States and Canada, and is being conducted as a public-private partnership with GlaxoSmithKline, using DMID clinical sites. In addition, single-project grants and contracts support therapeutic evaluations for a number of other diseases.

Potential Directions for Future Research

In FY 2005, DMID requested a study by the National Academy of Sciences (NAS) to explore potential new directions in the study of antimicrobial therapeutics. As a part of this study, the NAS hosted two workshops in 2005: one on the potential targets within immunomodulatory/host-mediated response pathways that could yield broad-spectrum antimicrobial therapies and another on potential new classes of antimicrobials based on pathogen metabolic pathways. When completed, the findings of this study will provide insight into promising new avenues of research in the field of antimicrobial/anti-infective development.

Division of Allergy, Immunology, and Transplantation

The Division of Allergy, Immunology, and Transplantation (DAIT) supports research and development for drugs and biologics to treat and prevent diseases mediated by the immune system, such as autoimmune diseases; primary immunodeficiencies; asthma and allergic diseases; and rejection of transplanted organs, cells, and tissues. DAIT has established several collaborative research groups to study the molecular and immunologic mechanisms that underlie the effects of immunotherapeutic agents currently being evaluated in clinical trials.

Several investigations to evaluate new and potentially more effective therapies for asthma and allergic diseases are currently underway, including immune-based therapies and the development of new medications that inhibit or stimulate specific immune system biochemical systems. DAIT-supported Autoimmunity Centers of Excellence are performing pilot clinical trials for several new immunomodulatory approaches to the prevention and treatment of autoimmune diseases. Researchers in these centers have expertise in various autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and type 1 diabetes.

DAIT supports several clinical trials programs that test candidate therapies to limit immune-mediated morbidity and mortality of organ transplantation. These programs evaluate novel immunomodulatory strategies to prevent acute rejection and chronic graft loss. Strategies being

examined include biological inhibitors of immune system activation, drug avoidance or minimization regimens to reduce problems associated with the immune system suppression needed to prevent rejection, and pre-transplant induction therapies to facilitate organ transplantation, prevent acute rejection, and promote immune tolerance. Through the Cooperative Clinical Trials in Pediatric Transplantation program, investigators are evaluating these strategies in children needing kidney transplants. DAIT and DAIDS cosponsor the Solid Organ Transplant in HIV program, which is implementing a multicenter prospective cohort study of kidney and liver transplantation in people with HIV. Before the availability of highly active antiretroviral therapy (HAART), HIV-positive patients often were not considered for transplants on the basis of poor prognosis. HAART has significantly increased the longevity of HIV-positive patients, with a subsequent increase in the number of HIV-positive patients with end-stage kidney or liver disease as potential candidates for transplantation. In FY 2004, DAIT established the Clinical Trials in Organ Transplantation program with cosponsorship from the National Institute on Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung, and Blood Institute to develop and implement interventional and observational clinical studies, accompanied by mechanistic studies, designed to enhance the understanding of and ultimately reduce the immune-mediated morbidity and mortality of organ transplantation. In FY 2004, DAIT and NIDDK launched the Clinical Islet Transplantation program, an international consortium that will design and implement human islet transplantation studies for improved treatment of type 1 diabetes. This consortium will develop and implement single- and/or multicenter clinical studies, accompanied by mechanistic studies, in islet transplantation with or without accompanying kidney transplantation, for the treatment of type 1 diabetes.

DAIT, in collaboration with NIDDK, supports the Nonhuman Primate Transplantation Tolerance Cooperative Study Group. The goal of this program is to evaluate the safety and efficacy of new ways to induce immune tolerance of transplanted tissue, using preclinical models of kidney and islet transplantation. Scientists in this study group have demonstrated long-term graft acceptance using tolerogenic regimens in both kidney and islet allograft recipients. In FY 2005, the program expanded the scope of transplantation models to include nonhuman primate models of heart and lung transplantation and will also provide an opportunity for critical preclinical research to complement NIAID-supported transplantation clinical trials. The program's previous expansion allowed more tolerance-induction strategies to be rigorously evaluated, improved sharing of valuable resources, and helped to forge new collaborations. To further accelerate the research conducted through this program, DAIT supports breeding colonies of specific pathogen-free rhesus and cynomolgus macaques.

DAIT, with cosponsorship from NIDDK and the Juvenile Diabetes Research Foundation International, continued to support the Immune Tolerance Network (ITN). ITN is an international consortium dedicated to the clinical evaluation of novel, tolerance-inducing therapies for autoimmune diseases, asthma and allergic diseases, and the prevention of graft rejection. The goal of tolerance-inducing therapies is to re-educate the immune system to eliminate harmful immune responses and graft rejection without reducing protective immunity to infectious agents. An important goal of ITN is to explore the immune mechanisms that cause candidate drugs to succeed or fail. ITN membership includes approximately 80 basic and clinical scientists and physicians at more than 40 institutions in the United States, Canada, Europe, and Australia.

Division of Intramural Research

The Division of Intramural Research (DIR) focuses substantial resources on basic studies of the immune system; disease pathogenesis; and microorganism structure, replication, and transmission. These basic investigations, employing animal models and the newest technologies, are key to the discovery of new drugs to treat infectious and immunologic diseases.

Basic Research for Target Discovery

Basic research on the biology of an organism can lead to the identification of an enzyme, receptor, or other important molecule it needs for replication; these molecules then become prime targets for inhibitory drugs. For example, in 2005, DIR basic research revealed a new target for drug therapy of prion diseases, such as Creutzfeldt-Jakob disease in people and mad cow disease in cattle. DIR scientists found that a variant form of abnormal prion protein—one lacking an "anchor" into the cell membrane—might be unable to signal cells to start the lethal disease process. This research suggests that the blocking the interaction of disease-associated prion protein with membrane-anchored normal prion protein could be a useful target for drug treatment.[28]

Animal Models of Disease Pathways

Investigation of avian influenza in humans has shown that excessive inflammation might be responsible in part for the acute respiratory distress syndrome and multi-organ failure observed in many patients. Studies of similar disease processes in animal models allow scientists to decipher what biochemical pathways are involved and how they might be disrupted. To identify novel targets to reduce the lethal inflammatory responses accompanying severe respiratory virus infection, DIR scientists are studying the pneumonia virus of mice (PVM), which causes an inflammatory response similar to that seen in severe human respiratory diseases caused by influenza and respiratory syncytial virus (RSV); the latter is a virus that can cause severe illness in the very young and very old. By administering a biochemical to block this pathway along with the antiviral agent ribavirin, DIR scientists prevented the inflammatory response to PVM, which reduced illness and death in mice. Specific antiviral therapy in conjunction with blockade of this pathway could ultimately prove to be a useful approach to severe respiratory virus disease in humans.

New Technologies Speed the Discovery Process

New technologies allow more precise characterization of the activity of current drugs, which may lead to the development of more effective formulations. DIR scientists are continuing to uncover the basic modes of action of current TB medications in order to integrate this information with genomic and combinatorial chemistry methods to speed development of second-generation drugs based on similar modes of action. New DNA microarray-based tools for deciphering the molecular mechanisms of anti-tubercular drugs will greatly facilitate these studies. For additional information, see the "Tuberculosis" section on page 133.

Translating Laboratory Research to the Clinic

To promote translation of laboratory discoveries into products and practices that improve human health, clinical programs are integrated into several of the DIR laboratories. DIR clinician-scientists are conducting more than 80 clinical research protocols at the NIH Clinical Center. Many of these protocols are testing the efficacy of new drug therapies, for example:

- Adjuvant cytokine therapy to boost the innate immune response in pulmonary *Mycobacterium avium* complex infection;

- Separate trials of subcutaneous recombinant interleukin-2, interleukin-7, and leflunomide in HIV infection;
- Peginterferon Alpha 2a and ribavirin induction therapy for chronic hepatitis C in patients who are co-infected with HIV-1; and
- Omalizumab (Xolair) for reducing eosinophil counts and improving symptoms in patients with eosinophilic gastroenteritis.